

Guidance for prescribers of low dose once weekly methotrexate (MTX)

Low dose once weekly methotrexate (MTX) is the “gold standard” disease modifying anti-rheumatic drug (DMARD) to treat rheumatoid arthritis (RA), other inflammatory arthritis and other autoimmune conditions. Disease modifying means that it prevents or lessens joint damage.

High doses of MTX (i.e. doses >1000mg at a time) constitute chemotherapy. However, the low doses that are used as DMARDs (i.e. 5-25mg weekly), do not. Low dose MTX has been recommended and used in rheumatic conditions for more than 20 years and its long-term safety profile has been well established in multiple cohorts (1).

A recent publication in the Medical Journal of Australia (2) highlighted a number of deaths that had occurred associated with low dose MTX use. These were particularly in the setting of accidental daily administration. This has caused alarm among our patients and their families, as well some of the GPs and other health professionals with whom we work.

The authors of the MJA publication made some suggestions to reduce the risk of further deaths including further changes in packet size, mandatory weekly dosing labelling on packaging, improving education, and including alerts in prescribing and dispensing software. Rheumatologists agree clearer labeling would be a step forward. The ARA recommends a MTX prescription be written specifying the dose and day of the week that the tablet is to be taken e.g. “20 mg once a week on Monday.”

The PBS restriction for MTX 10 mg (pack size of 50 tablets) is for “*Patients requiring doses greater than 20 mg per week.*” We therefore recommend that the 10 mg (pack size 50 tablets) option only be used when a patient is taking > 20 mg MTX per week.

If the patient is requiring doses of 20 mg per week or less you should prescribe 10 mg (pack size 15 tablets). Numbers of repeats is another area for potential review. Your computer may default to 10 mg x 50 with 2 repeats or 15 x 10 mg with 3 repeats. It is unwise to provide patients with > 3 months of MTX without a failsafe mechanism to ensure patients adhere to the recommended haematology and biochemical monitoring that is recommended to minimise any risks to patients (i.e. typically 1 to 3 monthly).

An additional mechanism to optimise outcomes for patients on low dose MTX is concomitant use of folic acid. Since 2009, international consensus strongly recommends co-prescription of at least 5 mg folic acid per week to reduce the risk of adverse events when a patient is taking low-dose MTX (3). This can be administered as a daily dose (e.g. 1 mg folic acid daily except for the day MTX is taken) or weekly dose (e.g. 5mg folic acid on the day after MTX is taken). The way folic acid is prescribed varies between rheumatologists and no method has been shown to be superior to others.

Low dose once weekly MTX is an excellent treatment for RA and other autoimmune disease. However it needs to be treated with respect by prescribers and patients to minimise the risk of adverse effects and medication errors.

In summary our suggestions for prescribing MTX in rheumatic disease that may minimise the risk of adverse outcomes include:

- a) Write the specific MTX dose and the day of the week that it should be taken
- b) Think carefully about the number of tablets you prescribe
- c) Think carefully about the number of repeats you prescribe
- d) Ensure the folic acid prescribed is at least 5 mg per week
- e) Ensure regular monitoring of haematology and biochemistry (typically 1-3 monthly)

The recent article (2) reported an estimated 200,000 MTX scripts dispensed per year and seven fatalities where MTX had been taken for between 3 and 10 consecutive days instead of once weekly. The number of deaths reported from overdose over the 15 year period, which while tragic, remains very small.

When properly taken and monitored, the benefits of low dose MTX benefits, in terms of reducing joint damage and deformity, diminishing disability and preventing long term complications of RA, other inflammatory arthritis and other autoimmune conditions, such as premature ischaemic heart disease and osteoporosis, far outweigh its potential for harm.

References:

- (1) Yazici Y, *Long-term safety of methotrexate in the treatment of rheumatoid arthritis* Clin Exp Rheumatol 2010; 28 (Suppl. 61): S65-S67.
- (2) Cairns R et al. *A decade of Australian methotrexate dosing errors* Med J Aust 2016; 204 (10): 384.
- (3) Visser K et al *Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative.* Ann Rheum Dis 2009; 68:1086–1093.